REMARKS

Status of the Specification

The Abstract has been amended so that it does not contain legal phraseology: *i.e.* the word, "said," has been replaced with the word, "the."

No new matter has been added.

Status of the Claims

Claims 1-2, 5 and 8-13 are pending and amended; and claims 3-4, 6-7, 9-10 and 12-19 are canceled. Claim 20 is added.

Claims 1-2, 5 and 8-13 have been amended to improve grammar and to better comply with U.S. formalities.

Claim 1 and new claim 21 have been amended/added reciting the cognitive dysfunction of schizophrenia. Support for these amendments is found in the Specification at page 5, lines 1-3.

New claim 20 is similar to claim 1, but claim 20 recites that only a single active compound, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide is administered. Support for aspect of claim 20 is found, for instance, in the Examples on pages 7-17 of the instant Specification disclosing the results of phase II clinical trials conducted using the schizophrenia treatment methods of the invention. Support for the reciting a "preparation" is found, for instance, on page 6, lines 9-20, of the specification.

No new matter has been added.

1. The Specification

On page 3 of the Office Action, the Examiner requires correction of the abstract: *i.e.* the removal of the word, "said," as inappropriate legal phraseology.

Applicants have, as indicated above, amended the Abstract so that it recites the word, "the," instead of the word, "said."

2. Claim Rejections under 35 USC Section 103

On pages 3-5 of the Office Action, the Examiner rejects claims 1-13 as allegedly obvious over Somerville et al. (W0 03/066039) in view of Wong et al. (USPN 6,964,962). Applicants respectfully traverse.

2.1 The Factual Foundation of the Obviousness Rejection is Inaccurate

As noted by the Examiner, Somerville et al. teaches that the instantly claimed active compound, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide (a.k.a. SM-13496) may be used to treat schizophrenia. (Office Action, pages 3-4). As admitted by the Examiner, Somerville et al. does not teach any dose of SM-13496 for treating schizophrenia. (Office Action, page 4). Applicants find that the Examiner has accurately described these teachings of Somerville et al.

But Applicants respectfully submit that the Examiner has mischaracterized the teachings of Wong et al. In particular, the Examiner states that Wong et al. teaches treating schizophrenia with a dose of 0.05 to 7500 mg/day/patient of SM-13496. (Office Action, page 4). But an accurate reading of Wong et al. reveals that Wong et al. does not actually teach treating any schizophrenic with any particular amount of SM-13496. In addition, a complete reading of Wong et al. reveals that it entirely contemplates treating schizophrenia by administering a **combination** of at least two (2) distinct types of active agents: (i) norepinephrine reuptake inhibitors and (ii) neuroleptic agents. (Wong et al., Column 5, lines 7-12).

Wong et al. expressly teaches that the **combination** of norepinephrine reuptake inhibitors and neuroleptic agents is necessary when treating schizophrenia because the co-administration of a norepinephrine reuptake inhibitor with a neuroleptic agent reduces serious and deleterious side effects caused by the administration of a neuroleptic agent alone. (Column 5, lines 1-4 and Column 10, lines 8-12). In particular, Wong et al. teaches that the side effects caused by typical neuroleptic agents include extrapyramidal symptoms, allergic reactions, weight gain, high body temperature and low blood pressure. (Wong et al., Column 3, lines 1-43). Wong et al. teaches that the side effects caused by atypical neuroleptic agents include agranulocytosis, sleepiness, weight gain, dizziness and increased risk of sudden cardiac death. (Wong et al., Column 4, lines 5-49).

2.1 The Examiner Improperly Relies on *In re Aller*

On page 4 of the Office Action, the Examiner attempts to justify the instant obviousness rejection by relying on the *In re Aller* rule that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454,456, 105 USPQ 223, 235 (CCPA 1955). The Examiner asserts that, because "Wong et al. teach 0.05 to 7500 mg/day/patient of [the instantly claimed compound] can be used to treat schizophrenia ... it would be obvious for one skilled in the art that the amount of SM-13496 may be optimized to be administered at [the instantly claimed dose ranges]." (Office Action, page 4).

As discussed above in Section 2.1, Wong et al. does not teach treating a schizophrenic with any particular dose of SM-13496. Instead, Wong et al. speculates that a dose of SM-13496 somewhere between 0.05 and 7500 mg/day/patient could be administered in **combination** with a norepinephrine reuptake inhibitor. But Applicants point out that there is a 150,000 fold difference between the minimum and maximum doses of the alleged "range" of SM-13496 doses. Moreover, the minimum intolerable dose of SM-13496 is 520 mg/day (See Declaration of Masaaki Ogasa, attached, a signed copy to be filed in a Supplemental Amendment); so the maximum dose of the alleged "range" taught by Wong et al. is almost 14x higher than the greatest amount of SM-13496 that should be given to a patient. And the minimum dose of SM-13496 required to have any therapeutic effect is 5 mg/day (See Declaration); so the minimum

dose of the alleged "range" taught by Wong et al. is 100x below the minimum amount that should be administered to a patient. It follows that the maximum and minimum doses of SM-13496 suggested by Wong et al. for combination schizophrenia therapy cannot be reasonably characterized as teaching a "range" of doses, but rather amounts to an uninformative and inaccurate speculation that covers more than the entire spectrum of amounts of SM-13496 that should be administered.

In addition, Applicants point out that, because Wong et al. entirely contemplates treating schizophrenia by administering a **combination** of norepinephrine reuptake inhibitors and neuroleptic agents, its entire disclosure is outside of the general conditions" of the schizophrenia treatment methods of the instant invention.

In view of the foregoing points and discussion, Applicants submit that Wong et al. does not teach a "range" of SM-13496 and that Wong et al does not meet the "general conditions" of the schizophrenia treatments of the present invention. Accordingly, the Examiner's reliance on *In re Aller* is of no avail in attempting to justify the instant obviousness rejection. Moreover, the Examiner has not established *prima facie* obviousness because neither Sommerville et al. nor Wong et al. teach the administering the 5 – 120 mg of the SM-13496, as recited in the instant claims. The obviousness rejection is therefore improper.

2.3 <u>The Instantly Claimed Methods for Treating Schizophrenia Provide Surprisingly Improved Results</u>

2.3 (a) *The Unexpected Lack of Negative Side Effects Provided by the Instantly Claimed Methods for Treating Schizophrenia*

In addition to mischaracterizing the teachings of Wong et al., the Examiner mischaracterizes the teachings of the instant specification by alleging that a showing of unexpected results is absent therefrom. (Office Action, page 4). As described above, Wong et al. teaches that weight gain is a side effect of treating schizophrenia with an atypical neuroleptic agent. (Column 4, lines 24-26). Wong et al. further teaches that treating schizophrenia by the co-administration of a norepinephrine reuptake inhibitor together with a neuroleptic agent minimizes the incidence of

weight gain. (Column 10, lines 14-18).

In contrast, the instant specification discloses that the presently claimed methods for treating schizophrenia by the daily administration of 5 to 120 mg of active compound defined by formula (1) is not only successful for the treatment of schizophrenia, but also provides unexpectedly advantageous results of not being accompanied by the side effects of body weight gain, bulimia, impotence, erectile dysfunction and convulsion. (See, for instance, the instant specification at page 12, lines 14-18). It follows that the instant specification indeed discloses that the presently claimed methods for treating schizophrenia provide surprisingly improved results over the prior art, which further establishes the non-obviousness of the instant claims and the impropriety of the instant obviousness rejection.

2.3 (b) *The Unexpected Amelioration of the Negative Symptoms of Schizophrenia Provided by the Instantly Claimed Methods for Treating Schizophrenia*

Applicants point out that, at the time the instant patent application was filed, the dogma in the field of schizophrenia therapy was that atypical neuroleptic drugs, such as SM-13496, were ineffective at treating the negative symptoms of schizophrenia. As evidence of this state of the art, Applicants direct the Examiner's attention to Erhart et al. (2006), Laughren and Levin (2005), Alphs (2006) and Kane (2005) and Kirkpatric et al. (2005) submitted together with this paper. (Exhibits 1-5) These references state that, even three years after the 2002 priority date of the parent application, a treatment for schizophrenia that addresses the negative symptoms of the disease was not available on the market.

But the instantly claimed schizophrenia treatment methods effectively ameliorate both the positive and negative symptoms of schizophrenia by administering SM-13496. Here, Applicants direct the Examiner's attention to the disclosure of the phase II clinical trials on pages 7-16 of the specification and the data set forth in the two (2) poster presentations by Ogasa et al., attached as Exhibit 6 which disclose that the instantly claimed schizophrenia treatment methods provide for the amelioration of the negative affects of schizophrenia.

Because, prior to the instant invention, the dogma in the field of schizophrenia therapy was that

atypical neuroleptics were ineffective at treating the negative symptoms of schizophrenia and because the instantly claimed schizophrenia treatment provides for the effective treatment of the negative symptoms of schizophrenia, the instantly claimed treatment methods provide surprisingly improved results, which further establishes the non-obviousness of the instant claims and impropriety of the instant obviousness rejection.

2.4 Conclusion

For at least the foregoing reasons, Applicants submit that the Examiner has failed to establish *prima facie* obviousness against the presently pending claims over the prior art of record. In addition, Applicants have established that the instant specification discloses evidence of surprisingly improved results provided by the presently claimed methods for treating schizophrenia. Accordingly, Applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection.

3. Conclusion

Applicants would like to thank the Examiner for granting an interview to be held at 2 pm (Eastern) on Thursday, June 26.

In view of the foregoing amendments and remarks, Applicants respectfully request immediate allowance of the claims, which define subject matter that meets all statutory patentability requirements.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petitions for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Registration No 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: June 17, 2008

Respectfully submitted,

By 30,330

Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive
Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicant